REMARKS:

Reconsideration of the present application is respectfully requested for the reasons that follow.

Objections to the Specification and Claims

The Examiner has objected to the specification for failing to include a Brief Description of the Drawings section. Applicants note that such a section does appear in the specification; specifically at p. 15, ll. 1-28. However, that section is titled "Figures." Accordingly, Applicants have amended the specification, as discussed above, to change the title to "Brief Description of the Drawings." Further, Applicants note that the figures are discussed in greater detail elsewhere in the specification (e.g., the examples). Therefore, this objection has been obviated and should be withdrawn.

The Examiner has also objected to claim 31, which is directed to steps i), ii) and iv). Claim 31 has been cancelled, this obviating this objection.

Claim Amendments

Claim 31 has been cancelled.

New claims 32-35 have been added. Each of these claims present slightly different language than claim 1. Written description support for these amendments can

be found in claim 1 and in the specification (throughout) as filed. No new matter is added.

Claim Rejections under 35 USC § 112, second paragraph

The Examiner has rejected claim 31 under 35 USC § 112, second paragraph, as being indefinite. Specifically, the Examiner argues that claim 31 recites that the first fusion protein is a phage coat protein, but that it is unclear how a phage coat protein can be a fusion protein. Claim 31 has been cancelled. Therefore, this rejection is obviated and should be withdrawn.

Claim Rejections under 35 USC § 102(b)

The Examiner has rejected claims 1, 3-7, 9 and 31 under 35 USC § 102(b) as being anticipated by Crameri (*Gene*, vol. 137, 1993, pp. 69-75). Crameri is directed to a cloning and expression system allowing the display of cDNAs on the surface of a filamentous phage which utilizes the interaction between leucine zipper proteins. The Examiner argues that Crameri teaches a first fusion protein PIII comprising a Jun-Leucine-Zipper domain and a pelB signal sequence, as well as a second fusion protein derived from a cDNA from a cDNA library, comprising a Fos-Leucine-Zipper domain and a pelB signal sequence. The Examiner argues that a mixture of these two fusion proteins anticipates the subject matter of independent claim 1. In arriving at this

conclusion, the Examiner reads the "folding state" elements out of claim 1, arguing that these limitations cannot be given patentable weight as there are no specific structures providing different folding requirements in the claims. Applicants traverse.

Applicants reiterate the arguments presented in response to the March 26, 2010 Office Action. Briefly, Applicants note that the claims do provide a structure (i.e., a stretch of amino acids) which provide a specific function (i.e., translocation). Therefore, the "folding state" elements should be given patentable weight. Further, Applicants have added new claims 32-35, each with a slightly different phrasing of the "folding state" limitation which highlights the structural features of the translocation sequence. The anticipation rejection based on Crameri should also not apply to new claims 32-35 for the same reasons as it should not apply to claim 1. The rejection of claim 1 should be withdrawn.

Claim Rejections under 35 USC § 103(a)

The Examiner has rejected claims 1, 3-9 and 31 under 35 USC § 103(a) as being obvious over Crameri (*Gene*, vol. 137, 1993, pp. 69-75) in view of Weiner (US Pat. No. 6,335,178) and further in view of Wu (*Arch. Microbiol.,* vol. 173, 2000, pp. 319-324). Crameri is discussed above. Weiner is directed to compositions and methods for secretion of functional proteins in a soluble form in host cells. Wu is directed to the membrane targeting and translocation of periplasmic and membrane-bound bacterial hydrogenases. The Examiner has also rejected claims 1 and 3-9 under 35 USC §

103(a) as being obvious over Crameri (*Gene*, vol. 137, 1993, pp. 69-75) in view of Georgiou (US Pat. No. 7,419,783). Crameri is discussed above. Georgiou is directed to leader peptides which direct export of heterologous proteins from the bacterial cytoplasm.

The Examiner argues that Crameri is the closest prior art to the subject matter Jun-Leucine-Zipper domain and a Fos-Leucine-Zipper domain, respectively, and a pelB signal sequence, which leads to the transport in an unfolded state into the periplasm. Further, the Examiner argues that Weiner in view of Wu, or Georgiou teach such a translocation sequence by disclosing a Tat-dependent translocation sequence which allegedly motivates the skilled person to modify the protein mixture of Crameri by introducing a Tat-dependent signal sequence in one of the fusion proteins. Hence, the subject matter of claim 1 is considered obvious.

Crameri teaches a first fusion protein comprising i) PIII, ii) a Jun Leucine zipper interaction domain and iii) wherein PIII is the phage coat protein comprising the pelB signal sequence, and a second fusion protein comprising i) a cDNA from a cDNA library, ii) a Fos Leucin zipper interaction domain and iii) a pelB signal sequence, wherein the interaction domain of the first fusion protein can bind to those of the second fusion protein. The Examiner argues that there is no structural limitation in claim 1 which corresponds to the translocation sequence, as no specific core structure is listed in the specification. Since there is no claimed structure corresponding to the claimed translocation sequence, the Examiner argues that this limitation can be rendered

obvious by any prior art showing any translocation sequence. It would thus, have been obvious to combine the above stated documents and to replace one known translocation sequence with another known translocation sequence, especially as Crameri would encourage inventors to be creative and to consider alternative options. Applicants traverse.

New claims 32-35 specify that the first fusion protein is translocated through the plasma membrane in an essentially unfolded state and the second fusion protein is translocated through the plasma membrane in an essentially folded state. Thereby, structural limitations to the claimed subject-matter are provided. Accordingly, Crameri does not render obvious the claimed subject matter as the skilled person would not replace a protein translocation sequence which is used for the transport of unfolded proteins, by a protein translocation sequence which is only used for the transport of folded proteins.

Starting from Crameri, a skilled person might have considered replacing the protein translocation sequence of PelB with a sequence which also causes the transport of unfolded proteins through the plasma membrane. The present application describes in detail that proteins being transported in a folded or unfolded state, cannot necessarily be transported in the respective different state, too (see p. 2, l. 19 to p. 3, l. 8). Thus, it would not have been obvious to the skilled person to recognize a protein translocation sequence using a different transportation mechanism, namely the transport of folded

proteins instead of unfolded proteins, as being equally suitable. The skilled person dealing with the transport of unfolded proteins, as described in Crameri, would not have considered replacing the known protein translocation sequence PelB with a translocation sequence that transports folded proteins. Thus, there was no motivation for the skilled person to combine Crameri with either Weiner and Wu, or with Georgiou.

Furthermore, the invitation in Crameri to be creative cannot be considered as being relevant to the assessment of obviousness. In fact, Crameri does not at all recognize that it may be desirable to translocate folded and unfolded proteins through the cytoplasmic membrane. Accordingly, Crameri does not provide any hint as to which translocation sequence to use alternatively. From the Crameri disclosure, one of skill in the art would have been motivated only to create a fusion protein where each individual protein is translocated through the plasma membrane in an unfolded state. Nothing in Crameri suggests that both of the individual proteins can be translocated through the plasma membrane in a folded state. Furthermore, absolutely nothing in Crameri suggests that the fusion protein could be created from a mixture of proteins, where one is transported folded and the other is transported unfolded. None of Weiner, Wu or Georgiou remedy this deficiency. Accordingly, the independent claims are non-obvious over Crameri in combination with either Weiner and Wu, or with Georgiou.

The Examiner further argued that the functional limitation of the first and second fusion protein being able to bind to each other would have been obvious to the skilled

person as it is known from the cell-free expression system in US patent 5,593,856 that protein binding is not required to take place in any particular localization.

US patent 5,593,856 relates to the production of proteins in cell-free extracts on a large scale. Further, the system described represents an artificial *in vitro* system of protein production. In contrast, the present application relates to an *in vivo* system. Accordingly, both systems cannot be compared, as *in vitro* and *in vivo* systems inherently require very different conditions.

Furthermore, the US patent 5,593,856 does not disclose the binding of two proteins in such a system. On the contrary, example 7 disclosed as a particular advantage of the invention, the possibility to avoid undesirable modifications appearing in *in vivo* systems due to the absence of post-translational modifications (see col. 9, ll. 28-35), which also include the covalent or non-covalent binding of proteins. Thus, a binding of two fusion proteins as described in the present claims does not occur in the method of producing proteins as disclosed in US patent 5,593,856.

Even if covalent or non-covalent binding of proteins would occur in the method disclosed in US patent 5,593,856, it is noted that the method of US patent 5,593,856 involves in a first step the preparation of a cell-free extract by rupturing cultured cells, e.g., via ultra-sound (see example 1, col. 7, ll. 18-21). Thereby the natural compartments of the cell are destroyed, bringing proteins into close proximity that are normally separated in different compartments. The only binding possible to occur is,

thus, an arbitrary binding between proteins randomly present in the lysate without these proteins fulfilling any common function. In contrast, the present application discloses two fusion proteins which are transported via different mechanisms into one compartment where they bind covalently or non-covalently to each other in order to fulfill a concerted function. Thus, the localization of the protein binding is important as a binding in a different compartment, e.g., the cytoplasm, would prevent them from fulfilling their function. Accordingly, the localization of the protein binding is not irrelevant but an essential part of the present invention. As such, the obviousness rejections should be withdrawn as to the rejected claims, and not applied as to the new claims.

In view of the foregoing, it is submitted that the present application is now in condition for allowance. Reconsideration and allowance of the pending claims are requested. The Director is authorized to charge any fees or credit any overpayment to Deposit Account No. 02-2135.

Respectfully submitted,

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